Editorial

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The future of molecular imaging in paradigm shift from reactive to proactive (P4) medicine: predictive, preventive, personalized and participatory

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Introduction

Over the past few decades medicine has been changing rapidly. For a long time the medical field relied primarily on evidence-based medicine, which focused on data from clinical trials [1]. In contrast, the medicine of the future will be based on presymptomatic indicators, a wellness-maintenance system, several measurements – including different numbers of 'OMICs', e.g. genomics, proteomics – individual-centric needs, the social networking of patients, and the genotype and phenotype of diseases [1].

In the 21st century, the terms personalized medicine, precise medicine, genomic medicine and even personal radiology have been used frequently [2]. Personalized medicine ensures that patients receive the right treatment at the right dose at the right time, with minimum adverse consequences and maximum efficacy [3]. As personalized medicine becomes more practical, image-guided biopsies will be integral for facilitating predictive and pharmacodynamic molecular pathology. Meanwhile, imaging has an important role in precise medicine [3]. Progress in diagnostic procedures, genomics and proteomics allows a window into subcellular mechanisms [3]. Personalized medicine ensures that clinical decisions are made according to a patient's molecular profile. Numerous crucial markers of diseases have already been accepted into standard practice [4]. For example, molecular imaging with a tissue biomarker will help in the discovery of novel drugs and also in predictive biopsies [4,5]. Furthermore, response to therapy has a multifaceted link to genotype, dysregulation of signalling conduits using gene expression, protein activity, protein–protein interactions and disease phenotypic traits. It is possible to gather these data with molecular imaging as well as with other established techniques, but imaging is problematic with thousands of low-specific markers [6].

Regarding the 'holy trinity' consisting of new technologies, new analytical tools and systems biology, molecular imaging requires advances in hardware and software to perform more complex mathematical and computational analyses [7].

Systems biology, health and disease

Systems biology, with its holistic approach to discovering important principles in biology (complex system) and the enabling technologies in genomics, proteomics, single-cell analysis, microfluidics and computational strategies, empowers a comprehensive approach to medicine [8,9]. Systems medicine originates in the perception that disease develops as a consequence of one or more disease-perturbed networks and these networks are dynamically altered during the course of the disease [3,7].

There are several networks working in the context of an individual's body, such as genetic networks, molecular networks, cellular networks and organ networks, which must be considered to truly understand the systems view of disease [7,9]. However, there are many diseases that, despite having dissimilar forms of clinical manifestation, form part of the same network. Indeed, with this approach, the 'diseasome' has been introduced as the network of human diseases that share common genetic and molecular traits [8]. Exactly how the networks are perturbed, and how these perturbed networks are dynamically altered, can be better understood by using high-throughput measurement technologies [3].

In addition, because of the dynamic situation of human health and disease resulting from changing biologic network architectures (genes, mRNAs, microRNAs, proteins and metabolites) and also nodal elements, it is not enough to have a static image of the system. Rather, it is necessary to have a dynamic model, as can be achieved with molecular imaging modalities, that captures the development of the biological complexity in healthy and unhealthy conditions before and after therapeutic intervention [8]. Labelled agents that are particular for the biologic processes could be applied for molecular imaging even before symptoms develop [8].

General picture of P4 medicine

Medicine is now experiencing a major revolution that will transform the nature of healthcare from a reactive to a proactive approach [9–11]. In the next few years, it will progressively transition to personalized, predictive,

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preventive and participatory medicine (P4 medicine) [12,13]. The revolution will be catalysed by the advances made in the basic scientific fields – such as complete sequencing of the human genome, the progress in imaging modalities and also the application of concepts of engineering physics (such as scale-free networks and complex systems) [8].

This revolutionary concept of P4 medicine was developed by David Galas and Leroy Hood from the Institute for Systems Biology in Seattle [8], at which molecular imaging plays an important role [14]. P4 medicine, as the clinical face of systems medicine, which is a part of systems biology, has two main goals: to quantify wellness and to demystify disease [9,15].

Impact of P4 medicine on the healthcare system

P4 medicine seems to present several advantages for the healthcare system – for example, the possibility to obtain and process billions of data sets for each individual, the gathering and analysis of longitudinal data for each individual, the stratification of patients into disease groups and improvement of the drug development process through the detection of new therapeutic target hubs [8,16].

P4 challenges

Although technology has advanced significantly in the last few decades, new advances are still needed for P4 medicine from bench to beach: (a) methods for sequencing of personalized genomes; (b) microfluidic methods and analysis of individual cells; (c) new computational techniques for the development of predictive models of the networks and dynamic interactions between the biological components, which is based on the incorporation of high-throughput OMIC information (transcriptomics, proteomics, metabolomics, lipidomics, etc.); (d) teaching patients and physicians about P4 medicine; and (e) new molecular imaging techniques. Although technology is developing quickly, integrating such acquired data with all other measurement data is a considerable challenge.

P4 medicine in the context of molecular imaging

Personalized: P4 medicine will be 'personalized' as it will be based on the genetic and epigenetic data of each individual. Personalized or precision medicine can help in data mining of quantitative anatomy and biology, in targeted imaging/targeted therapy and also in the real-time monitoring of treatment response.

Molecular imaging could provide particular molecular profiles and aid in the selection of the most effective treatment with the least toxicity on an individualized basis [17–19]. Imaging agents that have both diagnostic and therapeutic capabilities, or 'theragnostics,' would likely be more cost-effective and popular [20]. The great value of molecular imaging in personalized medicine is based on its ability to integrate metabolic and physiologic data with clinical phenotypes and prepare invaluable information about treatments.

Predictive: on average, one human differs from another by less than 1% of their genetic makeup. However, these genetic variances cause physical dissimilarities, such as the potential predisposition to different diseases [1]. Medicine will be 'predictive' as this personalized data will permit medical practitioners to determine the risk for specific diseases in each individual [19].

Imaging modalities will play a significant role as non-invasive screening procedures that are both sensitive and precise predictors of diseases [12]. Reports have revealed that only PET affected the management decisions in 38% of cancer cases [21].

Preventive: medicine will be 'preventive' as the prediction of risk will allow for the use of prophylactic procedures (lifestyle or therapeutic) to lessen this risk. In this context, it is widely accepted that molecular/genetic screening as well as intervention (often guided by imaging) is the most efficient approach to disease management [19]. Theranostic agents can also be implemented.

Participatory: it will be 'participatory' because most of these prophylactic manipulations will necessitate the contribution of the patient. This includes a range of participatory activities, such as sharing data, educating patients and physicians and also advising patients on personal choices related to illness and well-being. The growing use of social networks by patients, as well as the activities of patients' associations, are instances of participatory actions [19].

Current NIH programmes on P4 with emphasis on molecular imaging

P4 medicine is the future and has emphasized its role in future directions [14,22]. There are various programmes at the NIH that have been pursuing the concept of P4 medicine, including the current Molecular Libraries and Imaging programme [23]. It works on small molecules that can be useful as chemical probes to assess the functions of genes, cells and biochemical pathways in health and disease [24]. In this field, molecular imaging tracers will have a great impact [24–26], and it was mentioned 10 years ago that molecular imaging is one of top 10 technologies that will change the world [27,28]. More examples of ongoing NIH programmes in this area include the following: single cell analysis, metabolomics, genotype-tissue expression, illuminating the druggable genome and the big data to knowledge (BD2K) programme [23].

Radiogenomics

In addition, translational bioinformatics is one of the evolving fields that will help develop P4 medicine, as

well as some terms such as personal genome, metagenome, epigenome, genomics, pharmacogenomics, transcriptomics and metabolomics pertaining to this branch of science. These OMIC studies can be prepared by next-generation sequencing, which is a high-throughput technology based on informatics [double helix, Sanger sequencing/genome project (SNP)].

Radiogenomics, another OMIC study, is the integration of in-vivo imaging with large-scale gene expression profiles, which can show imaging heterogeneity mirroring biological heterogeneity [29]. The fusion of imaging tools with molecular techniques, such as functional genomic assays, offers the potential for the rapid clinical translation of powerful high-throughput technology [29]. Radiogenomics can create imaging biomarkers that can recognize the genomics of a disease, particularly cancer, without the use of a biopsy [6,30]. Numerous techniques are used to reveal correlations between MRI, CT and PET imaging features and the genomics of disease, such as large-scale MRI microRNA–mRNA correlative study in glioblastoma [31,32], liver cancer genome from non-invasive imaging features [33] and link image characteristics of non-small-cell lung nodules in CT scans to predict survival using gene expression data [29,34]. Recently, a radiogenomic study in incidentalomas was conducted [35].

There has been vast improvement in the performance of imaging modalities. For example, molecular imaging now provides a functional and dynamic read-out of in-treatments, from nanometre to entire body scale [4,36,37]. The multimodality imaging approach and the incorporation of multidimensional high-throughput 'OMICS' methods (accompanied by genetics/genomic data) would bridge the gap between our knowledge of fundamental mechanisms of disease processes and daily clinical practice [38]. Therefore, imaging doctors must learn genetic pathways and therapeutically target points in a new genetic world consisting of genetic data, clinical data and imaging features.

Most significantly, the future of practice and research will require network-connected and interdisciplinary teams of image professionals, clinicians, specialists familiar with the integrated analysis of both imaging and genetic data types, as well as physiochemists and molecular biologists [29]. In the future, the imaging doctor's role will be that of diagnostic data manager and coordinator, and not of image interpreter.

Bringing new scientific issues into clinical practice necessitates teamwork between academia and industry to develop new agents and carry out translational research [12]. Therefore, we should prepare a new training paradigm for tomorrow's colleagues to address the future of biomedical imaging.

Conclusion

Medicine is now experiencing a major revolution that will transform the nature of healthcare from reactive to proactive. It will progressively transition to personalized, predictive, preventive and participatory medicine (P4 medicine). In the meantime, ongoing technological advances, especially in the field of molecular imaging, and also interdisciplinary collaborations with various branches of science are mandatory for the implementation of P4 medicine. New training paradigms are necessary for tomorrow's colleagues to establish the conceptual bases and discuss the principal aspects of P4 medicine in the framework of molecular imaging and determine who will benefit from a deeper, more holistic view of illness by integrating pathophysiology-based models with emerging molecular mechanisms.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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